Psychopharmacologic Treatment of Children Prenatally Exposed to Drugs of Abuse

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Running Head: Pharmacotherapy with Prenatal Exposure

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Abstract

Objective: This pilot study compared the pharmacologic treatment history and clinical outcomes observed in pediatric outpatients with psychiatric disorders exposed to drugs of abuse *in utero* to those of an age-, sex- and psychiatric disorder-matched, non-drug-exposed group.

Methods: In this matched cohort study, medical records of children treated at an academic, child and adolescent psychiatry outpatient clinic were reviewed. Children with caregiver-reported history of prenatal drug exposure were compared to a non-drug-exposed control group being cared for by the same providers. Patients were rated with the Clinical Global Impressions –Severity scale (CGI-S) throughout treatment. The changes in pre- and post-treatment CGI-S scores and the total number of medication trials were determined between groups.

Results: The drug-exposed group (n=30) had a higher total number of lifetime medication trials compared to the non-drug-exposed group (n=28), and were taking significantly more total medications, at their final assessment. Unlike the non-drug-exposed group, the drug-exposed group demonstrated a lack of clinical improvement.

Conclusions: These results suggest that *in utero* drug-exposed children may be more treatment-refractory to or experience greater side effects from the pharmacologic treatment of psychiatric disorders than controls, although we cannot determine if early environment or drugs exposure drives these findings.

Introduction

Despite public health and individual provider efforts to decrease substance use among pregnant women (Gilbert et al., 2007; Polen, Whitlock, Wisdom, Nygren, & Bougatsos, 2008; Pomeroy & Steiker, 2012; Svikis & Reid-Quinones, 2003), recent data suggest this remains a widespread problem. Among 15- to 44-year-old pregnant women, 4.4% reported current use of illicit drugs, 10.8% reported current alcohol use and 16.3% reported cigarette use within the past month (U.S. Department of Health and Human Services, 2011). Drug and alcohol use in pregnancy is thought to be a significant contributor to the development of cognitive (Fried, Watkinson, & Gray, 1998; Jacobson, Jacobson, Sokol, Martier, & Ager, 1993) and psychiatric impairment (Huestis & Choo, 2002; Nair, Black, Ackerman, Schuler, & Keane, 2008) in exposed offspring. In particular, prenatal drug exposure has been associated with antisocial/disruptive behavior, impulsivity, attention problems, aggression and anxiety (Irner, 2012; Minnes, Lang, & Singer, 2011; Williams & Ross, 2007). Children exposed to drugs of abuse during the prenatal period are also vulnerable to attachment failures (Goodman, Hans, & Cox, 1999; O'Connor, Kogan, & Findlay, 2002), maltreatment (Kelley, 1992; Smith & Test, 2002; Sun, Freese, & Fitzgerald, 2007) and the other sequelae of ongoing parental drug use (Bartu, Sharp, Ludlow, & Doherty, 2006; Smith & Test, 2002). Animal models suggest that the presence of drugs of abuse during the prenatal period may be neurotoxic (Carneiro et al., 2005; Friedman & Wang, 1998; Lidow & Song, 2001) and may disrupt neurotransmitter systems relevant to mechanisms of action of psychopharmacological treatments (Simansky & Kachelries, 1996). Results suggest that exposed animals self-administer more of the drug they were exposed to prenatally, in addition to other drugs of abuse (Malanga & Kosofsky, 2003). Drug-exposed youth may experience atypical or ineffective responses to pharmacologic treatment, but there has been no research to date to

address this in humans. The existing literature also fails to provide any guidance to clinicians regarding this commonly encountered presentation.

In human brain imaging studies (mean age = 8.2 years), prenatal cocaine exposure has been associated with decreased volume in some subcortical regions, including regions with prominent dopamine innervation, such as the putamen (Bhat & Baraban, 1993), as well as decreased cortical volumes in the occipital and parietal lobes (Dow-Edwards et al., 2006; Lewis et al., 2004; Rivkin et al., 2008). With prenatal exposure to methamphetamine, volumetric imaging studies in children (mean age = 7.4 years) also found decreased subcortical volumes, particularly in the putamen, globus pallidus and hippocampus (Chang et al., 2004). *In utero* exposure to alcohol has been better studied and found to be associated with diffuse decreased cerebral and cerebellar volumes (mean age = 13 years) (Sowell et al., 2001), especially in regions related to verbal learning and executive functioning (Bookstein, Streissguth, Sampson, Connor, & Barr, 2002; Sowell, et al., 2001). Thus, drugs of abuse during the prenatal period have been associated with neurobiological changes across cortical and subcortical regions in children, typically in the direction of abnormally small structural volumes. Given these brain abnormalities, multiple neurotransmitter systems are likely affected by prenatal drug exposure. Therefore, we hypothesized that across classes, psychotropic medications may be less effective in individuals with prenatal drug exposure, given the potential impact across neurotransmitter systems.

The purpose of this pilot study was to evaluate whether response to psychopharmacological treatment is less effective in children with prenatal drug exposure, compared to psychiatrically similar outpatients without a history of prenatal drug exposure. In addition, we sought to determine if any patterns of psychotropic medication administration exist that differentiate these two groups. Finally, based on the suspected neurobiological impact of *in utero* drug exposure, we assessed if drug-exposed children were less responsive

to treatment with all classes of psychotropic medications, as evidenced by the total number of trials of medication initiated.

Methods

Sample

This matched cohort pilot study consisted of an Institutional Review Board (IRB) approved review of outpatient psychiatric records of 58 children and adolescents seen at a Child and Adolescent Psychiatry Outpatient Clinic at an academic medical center. The *in utero* drug-exposed cohort was selected from children ages 3- to 18-years-old who were referred to study personnel by their treating psychiatrist at the study site because of reported prenatal drug exposure. Their chart was reviewed by a research assistant blind to the study's intent to ensure the following inclusion criteria: presence of DSM-IV-TR Axis I diagnosis (American Psychiatric Association (APA) 2000), current and past psychotropic medication treatment and a caregiver report of a history of prenatal maternal misuse of one or more of the following: opiates, benzodiazepines, tobacco, alcohol, marijuana, stimulants, or unspecified polydrug use. Only one individual with isolated tobacco exposure was included. Three sibling pairs were included in the drug-exposed group. The non-drug-exposed psychiatric control group was selected from 3- to 18-year-olds who were also treated in the same clinic. A blinded research assistant, whose work was cross-checked for reliability, randomly selected charts from the entire clinic population under the clinical management of four psychiatrists by first matching for drug-exposure. Clinical information was collected from a three-year period. The subjects were then matched case-by-case for age, sex, psychiatric diagnoses (with the exception of reactive attachment disorder as discussed below), socioeconomic status (SES) and race. SES ratings (low, lower-middle, middle, or high) were a combination of health insurance and parental employment provided by the adult

accompanying the child to the appointment; a lower SES is coded with a lower score. Family status is coded as a child living with one biological parent, two biological parents, adopted, in foster care, or other, defined as anything outside of these classifications (e.g. living with grandparents or court-appointed guardians). Each chart was screened to ensure that the psychiatric controls did not have *in utero* drug exposure. From a review of non-psychotropic medications, the two groups were also matched on different physical health issues including asthma, allergies, epilepsy, and gastroesophageal reflux disease. Information on SES, family status, psychiatric diagnoses, previously used psychotropic medications, psychotropic medication changes throughout the study period and the psychotropic medications prescribed at each visit of the study period were collected and recorded. For inclusion, all cases were in treatment **at our center** for a minimum of one month. **The study period was limited to three years.** The last visit reported here indicates the last time point in which data was recorded, not necessarily the child's last treatment visit. Clinicians were unaware of plans for the chart review at the time of clinical management**.**

Measures

DSM-IV-TR diagnoses were determined by the treating child and adolescent psychiatrist through routine clinical assessments. For this study, the following diagnostic categories were coded: attention-deficit/hyperactivity disorder (ADHD; includes the hyperactive, inattentive and combined subtypes), oppositional defiant disorder (ODD), conduct disorder, other disruptive behavior disorders (disruptive behavior disorder not otherwise specified (NOS), intermittent explosive disorder, and pyromania), pervasive developmental disorders (pervasive developmental disorder NOS, Asperger's disorder, and autistic disorder), post-traumatic stress disorder (PTSD), reactive attachment disorder (RAD), anxiety disorders (generalized anxiety disorder, obsessive-compulsive disorder, and social anxiety disorder), mood disorders (major depressive disorder, dysthymic disorder, mood

disorder NOS, bipolar disorder and depressive disorder NOS), mental retardation, learning disorders (reading and specific learning disorders with impairment in writing or mathematics, and undefined learning disorders) and communication disorders (phonological disorder, expressive language disorder, and mixed receptive-expressive language disorder). Children with other DSM-IV-TR diagnoses did not present by chance in this sample, but were not intentionally excluded. **Participants with more than one diagnosis within the same category were noted to be a single case within that diagnostic category (see "Number of Cases with the Following Diagnoses;" Table 1).**

The classes of drugs of abuse for *in utero* exposure were classified as opiates, benzodiazepines, tobacco, alcohol, marijuana, stimulants (cocaine and methamphetamine) and unspecified polydrug use. Unspecified polydrug use includes a caregiver report that during pregnancy the biological mother used multiple unknown drugs.

Psychotropic medications that subjects were identified to be prescribed were coded as the following: atypical antipsychotics (aripiprazole, olanzapine, quetiapine, risperidone, and ziprasidone), alpha agonists (clonidine, guanfacine, and guanfacine ER), antidepressants (bupropion hydrochloride, citalopram, fluoxetine, fluvoxamine, imipramine, mirtazapine, paroxetine, sertraline, trazodone) anti-manic agents (carbamazepine, lamotrigine, lithium, oxcarbamazepine, and valproate), stimulants (dexmethylphenidate, dextroamphetamine/amphetamine, lisdexamfetamine, methylphenidate, and methamphetamine), typical antipsychotics (fluphenazine, haloperidol, and thorazine), anticholinergics (benztropine, diphenhydramine, and hydroxyzine), and other medications (atomoxetine, buspirone, clonazepam, melatonin, and molindone).

For each subject, the clinician-rated Clinical Global Impression–Severity scale (CGI-S) (Guy, National Institute of Mental Health (U.S.). Psychopharmacology Research Branch.,

& Early Clinical Drug Evaluation Program., 1976) was used as a metric for the patient's general clinical severity and was rated at each clinical encounter, coded as ordinal data on the following 7-point scale: 1 = Normal, not at all ill, 2 = Borderline mentally ill, 3 = Mildly ill, 4 = Moderately ill, 5 = Markedly ill, 6 = Severely ill, and 7 = Among the most extremely ill patients. We use change in CGI-S as a proxy for clinical improvement or decline.

Additional study outcome measures were: the total number of individual medications (behavioral, psychiatric) used throughout treatment at the clinic, the total number of individual medications prescribed at the last clinic visit included in this study period, the total overall number of medications used in the subject's lifetime up through the last visit, the total number of visits to the clinic, and the total number of individual medications in each medication class used during each subject's lifetime.

Data Analysis

Statistical analyses were conducted using SPSS version 20.0 (Chicago, IL: IBM; 2012). Independent samples t-tests were performed to compare groups on age, SES, number of psychiatric diagnoses and classes of the various psychiatric medications for the purposes of group matching. Chi-squared tests were performed to compare sex **and race (Caucasian vs. non-Caucasian) between** the two groups. Independent samples t-tests were also used to assess group differences on psychotropic medication-related outcomes. These included: the total number of outpatient psychiatric visits, **the number of months in treatment,** the total number of all types of psychotropic medications the subjects were taking at clinic intake, the total number of different medications prescribed throughout the subject's treatment course, the total number of medications prescribed at the final clinical assessment time point, the total number of psychotropic medications previously prescribed prior to presentation to our clinic or prescribed during treatment in our clinic, and the total number of medications

prescribed throughout the subject's lifetime in each medication class. An analysis of covariance (ANCOVA; covariates: RAD diagnosis and family status) was also performed for these same clinical outcomes to ensure that results were not impacted by group differences in RAD diagnosis and family status due to results mentioned below. Lastly, to evaluate differences between the intake visit and the last clinic visit, paired t-tests were performed for the drug-exposed and the non-drug-exposed groups separately for their initial and final CGI-S scores, the total number of medications they were prescribed at the intake and final visits and the number of medications prescribed by drug class. Significant within-group differences were also compared between groups. A threshold of $p<0.05$ was used to determine statistical significance. Corrections for multiple statistical comparisons were not undertaken given the small sample size and exploratory nature of this study.

Results

Table 1 provides demographic and clinical characteristics of the participants and the number of participants exposed *in utero* to a particular class of drug of abuse. The two groups were matched on age, gender, race, SES, and the number and types of psychiatric (except RAD) and medical diagnoses, as case-by-case matching in these variables was used to select the control group. The groups differed on the prevalence of RAD and family status. RAD was significantly more prevalent among the drug-exposed participants, although it was diagnosed in only 5 drug-exposed children. Regarding family status, more children in the drug-exposed group lived in a foster or adopted home. **Additionally, four control group participants had either an unreported or unknown family status.** The groups did not differ on baseline CGI-S scores (Table 2) or for the experience and training of the clinicians.

Clinical Outcomes

The drug-exposed and non-drug-exposed groups were compared based on various *a priori* defined clinical outcomes, as presented in Table 2. The two groups differed significantly on three of these outcomes. First, youth in the drug-exposed group were prescribed a greater number of psychotropic medications throughout their lifetime (mean = 5.87, standard deviation (SD) = 3.839) than the non-drug-exposed group (mean = 4.11, SD = 2.485; p = 0.044; effect size: Cohen's d effect size= 0.544). Second, the drug-exposed participants were prescribed significantly more psychotropic medications (mean = 2.30, SD = 1.264) at the last outpatient psychiatric clinic visit than the non-drug-exposed group (mean = 1.64, SD = 0.870; p = 0.026; Cohen's d = 0.608). Third, the reported final CGI-S score was higher (more severely ill) in the drug-exposed group (mean = 4.14, SD = 0.803) than the non-drug-exposed group (mean = 3.57, SD = 1.080; p = 0.033; Cohen's d = 0.599). CGI-S scores did not differ at baseline: drug-exposed group (mean = 4.32, SD = 0.670) and non-drug-exposed group (mean = 4.00, SD = 1.000; p = 0.177; Cohen's d = 0.376). There were no differences between the two groups on the total number of outpatient psychiatric clinic visits **or duration of treatment (during the study period),** the total number of psychotropic medications prescribed during the initiation of treatment at the clinic, or the number of medications prescribed throughout the subjects' lifetime, within each specific medication class. The results of the ANCOVA co-varying for RAD and family status were no different than the results of the independent samples t-tests presented in Table 2.

Table 3 details the changes in clinical outcomes between the two groups from the intake visit to the final clinic visit included in this study. For the non-drug-exposed group, three significant within-group differences were found: (1) The CGI-S scores were significantly lower (improved) at the final visit (p = 0.015); (2) the total number of psychotropic medications prescribed at the final visit of the study was significantly greater than the number of psychotropic medications prescribed at the intake visit (p = 0.006); and

(3) the number of stimulants prescribed at the final visit was significantly greater than at intake ($p = 0.001$). No differences were found for the number of atypical antipsychotics, alpha agonists, anti-manic agents, antidepressants, anticholinergics, or the other medication classes prescribed over the duration of treatment in the clinic. For the drug-exposed group, three significant within group differences were found: (1) the total number of psychotropic medications prescribed at the final visit in this study was significantly greater than the number of psychotropic medications subjects were taking at the intake visit ($p = 0.005$); (2) the number of atypical antipsychotics prescribed at the final visit was significantly greater than at intake ($p = 0.006$); and (3) the number of stimulants prescribed at the final visit was significantly greater than at intake ($p = 0.001$). There were no differences found for the CGI-S scores or for other classes of medications. Statistical analyses could not be performed on the difference in the number of subjects prescribed typical antipsychotics because the standard error of the difference was zero.

Group differences in the clinical outcomes between the intake visit and final visit are presented in Table 4. Only the four variables that showed significant within group differences were evaluated for between group differences. These variables include the CGI-S scale score, the total number of prescribed medications, atypical antipsychotics, and stimulants during treatment at the clinic. No significant differences were found among these variables in the between groups comparisons.

Discussion

This matched cohort pilot study was performed to gain a preliminary understanding of psychotropic medication use and response in children prenatally exposed to drugs of abuse. The primary finding in this study is that the total number of psychotropic medications prescribed throughout the lifetime of children with a history of *in utero* drug-exposure was significantly higher than reported in children without a history of *in utero* drug exposure. The

results suggest that children with *in utero* drug exposure may be more refractory to treatment with psychotropic medications than their non-drug-exposed peers. Drug-exposed youth also appear to be less responsive to pharmacotherapy compared to non-drug-exposed youth, as evidenced by the lack of significant improvement in clinical severity ratings while being prescribed an increased number of medications across time. Finally, we found that atypical antipsychotics and stimulants are prescribed at an increasing rate throughout the treatment course for *in utero* drug-exposed children, while stimulants alone are prescribed at a higher rate throughout treatment in the non-drug-exposed group. Overall, the magnitude of all measured clinical changes (initial vs. final visits) did not differ between groups.

The primary finding in this study is that the total number of psychotropic medications prescribed throughout the lifetime of children with a history of *in utero* drug-exposure was significantly higher than reported in children without a history of *in utero* drug exposure. It may be that these differences are based on the lack of significant improvement in target behavioral symptoms with psychotropic medications, the occurrence of more adverse effects of treatment, or both. It is worth noting that the initial clinical severity scores and number of psychiatric diagnoses at baseline did not differ between groups, suggesting that the drug-exposed group was not simply more psychiatrically impaired, thus requiring more complex psychopharmacology.

In addition to more lifetime psychotropic medication trials, drug-exposed children were also prescribed a greater number of medications at the final visit, compared to non-drug-exposed children. However, both groups were found to have more medications prescribed at the final visit than at the initial visit. This indicates that there is a general tendency to prescribe more medications as a result of treatment in an outpatient psychiatric clinic. We suspect that some clinically-relevant aspect of drug-exposed youth (i.e., refractory symptoms, adverse events) results in a larger number of individual medications prescribed

over time. The results indicate that, as a whole, drug-exposed children required more medications to help control their symptoms, supporting clinical anecdotes and our study hypothesis that medication regimens may be more complex in those with prenatal drug exposure. Given the diffuse changes to neurocircuitry resulting from *in utero* drug exposure, it is certainly plausible that receptor-level interactions with medications are abnormal and result in ineffective responses or adverse effects. Similarly, the CGI-S score was the same between the groups at intake, but different between the two groups at the final assessed visit, indicating that the non-drug-exposed group had less severe clinical impairment with pharmacological treatment over time. In addition, the drug-exposed group showed no significant change in symptom severity via the CGI-S score over time with medication treatment (mean = 0.179 CGI-S score improvement), whereas the non-drug-exposed did show significant CGI-S score improvement (mean = 0.435 CGI-S score improvement). Again, this finding underscores the notion that drug-exposed youth may be more refractory to treatments, although the magnitude of change across treatment was small for both groups and did not differ between the two groups.

It was also found that prenatally drug-exposed children were prescribed more atypical antipsychotics over the course of treatment. This difference was not observed across treatment for non-drug-exposed youth. Similarly, both non-drug-exposed and drug-exposed youth were receiving stimulant medications more often at the end of the study period than at the beginning. Combined, these findings raise the possibility that stimulants may be more helpful and/or better tolerated in these populations of children seeking outpatient psychiatric treatment, while atypical antipsychotics may be preferable in drug-exposed youth. Alternatively, clinicians may be moving to second- and third- line agents like atypicals due to lack of appreciable symptomatic improvement or tolerability with first line agents. However, direct between group comparisons of prescription changes to these medication classes across

treatment did not reflect these differences. Additional research in a larger sample is warranted to address this difference in clinician prescribing practices, as it may reflect important differences between groups in regards to insight into medication use, trends, and tolerability.

There are several limitations to this preliminary study. First, this study was designed to be a pilot evaluation of the relationships between pharmacotherapy and clinical responses in children exposed to drugs *in utero,* in order to guide future, larger-scale investigations in this area. Thus, the small sample size is a notable limitation. However, given the understudied clinical population and the lack of any prior studies investigating these relationships, the study remains of value. Second, assessments were not structured and treatment was naturalistic, subject to the biases of each clinician, as clinicians were not blinded to prenatal drug exposures. Differences in medication adherence and participation in counseling or therapy, for which this study did not have the infrastructure to monitor, could also be present. Third, exposure to *in utero* drugs was obtained only by the presenting caregiver's report and is therefore subject to errors or bias. In most cases, a biological parent was not the reporter, but when either biological parent accompanied the child to the clinic, there could have been an inclination by the parents to minimize or deny prenatal drug exposure, which could result in a drug-exposed subject being placed in the non-drug-exposed group. Similarly, we attempted to control for a number of confounding variables that could result in group differences, but, as the higher rates of RAD suggest, the drug-exposed youth were likely to be exposed to a range of challenges early in the child's life that were different from those in the non-drug-exposed group, despite their similar DSM-IV-TR diagnoses. These early life experiences likely impact brain development differently (Forns et al., 2012; McLaughlin, Fox, Zeanah, & Nelson, 2011; Sheridan, Fox, Zeanah, McLaughlin, & Nelson, 2012) as well as the development of psychopathology (Steinhausen, Mas, Ledermann, & Metzke, 2006), but to date, specific effects on psychopharmacologic responses have not been

reported. Additionally, the potential for confounding results based on maternal psychopathological differences, genetic or not, were not accounted for between the two groups. Thus, there may be reasons why some mothers are more likely to use drugs of abuse during pregnancy that confound the results. However, given that animal studies have been able to control for these differences and still find drug-induced neurobiological changes, further study is warranted. Fourth, the genetic confound of including three sibling pairs in the drug-exposed group was not accounted for given the preliminary nature of the study. Lastly, as with most research involving human participants and prenatal drug exposure, drug use during pregnancy was heterogeneous and diverse. Thus, no conclusions about the clinical impact of specific types of drugs of abuse can be made.

Conclusions

Prenatal drug exposure is common among children in psychiatric treatment (Johnson & Leff, 1999), but the impact of this *in utero* drug exposure on response to psychotropic medication treatment has previously been unexplored. In our pilot matched cohort study, drug-exposed children appear to be prescribed more psychotropic medications over their lifetime, based upon the data collected over the three-year treatment period of our study. Yet despite more medication trials, the drug-exposed group did not appear to experience associated clinical improvement. The increased number of prescribed trials of second or third line agents, such as atypical antipsychotics, also suggests the presence of refractory symptoms.

Animal models and human neuroimaging studies indicate that prenatal drug exposure does have long-term consequences on the neurobiological and behavioral development of children. The results of this preliminary study indicate that this exposure can result in more challenging psychotropic medication management, and that these children may be less

responsive to medications and/or more vulnerable to adverse effects. Additional investigation is needed to validate these findings and to determine if certain classes of psychotropic medications may potentially be more effective and better tolerated in these children.

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REFERENCES

Bartu, A., Sharp, J., Ludlow, J., & Doherty, D. A. (2006). Postnatal home visiting for illicit drug-using mothers and their infants: a randomised controlled trial. *Aust N Z J Obstet Gynaecol, 46*(5), 419-426.

Bhat, R. V., & Baraban, J. M. (1993). Activation of transcription factor genes in striatum by cocaine: role of both serotonin and dopamine systems. *J Pharmacol Exp Ther, 267*(1), 496-505.

Bookstein, F. L., Streissguth, A. P., Sampson, P. D., Connor, P. D., & Barr, H. M. (2002). Corpus callosum shape and neuropsychological deficits in adult males with heavy fetal alcohol exposure. *Neuroimage, 15*(1), 233-251.

Carneiro, L. M., Diogenes, J. P., Vasconcelos, S. M., Aragao, G. F., Noronha, E. C., Gomes, P. B., & Viana, G. S. (2005). Behavioral and neurochemical effects on rat offspring after prenatal exposure to ethanol. *Neurotoxicol Teratol, 27*(4), 585-592.

Chang, L., Smith, L. M., LoPresti, C., Yonekura, M. L., Kuo, J., Walot, I., & Ernst, T. (2004). Smaller subcortical volumes and cognitive deficits in children with prenatal methamphetamine exposure. *Psychiatry Res, 132*(2), 95-106.

Dow-Edwards, D. L., Benveniste, H., Behnke, M., Bandstra, E. S., Singer, L. T., Hurd, Y. L., & Stanford, L. R. (2006). Neuroimaging of prenatal drug exposure. *Neurotoxicol Teratol, 28*(3), 386-402.

Forns, J., Torrent, M., Garcia-Esteban, R., Caceres, A., Pilar Gomila, M., Martinez, D., . . . Sunyer, J. (2012). Longitudinal association between early life socio-environmental factors and attention function at the age 11 years. *Environ Res, 117*, 54-59.

Fried, P. A., Watkinson, B., & Gray, R. (1998). Differential effects on cognitive functioning in 9- to 12-year olds prenatally exposed to cigarettes and marihuana. *Neurotoxicol Teratol, 20*(3), 293-306.

Friedman, E., & Wang, H. Y. (1998). Prenatal cocaine exposure alters signal transduction in the brain D1 dopamine receptor system. *Ann N Y Acad Sci, 846*, 238-247.

Gilbert, P., Herzig, K., Thakar, D., Viloria, J., Bogetz, A., Danley, D. W., . . . Gerbert, B. (2007). How health care setting affects prenatal providers' risk reduction practices: a qualitative comparison of settings. *Women Health, 45*(2), 41-57.

Goodman, G., Hans, S. L., & Cox, S. M. (1999). Attachment behavior and its antecedents in offspring born to methadone-maintained women. *J Clin Child Psychol, 28*(1), 58-69.

Guy, W., National Institute of Mental Health (U.S.). Psychopharmacology Research Branch., & Early Clinical Drug Evaluation Program. (1976). *ECDEU assessment manual for psychopharmacology* (Rev. ed.). Rockville, Md.: U. S. Dept. of Health, Education, and Welfare, Public Health Service, Alcohol, Drug Abuse, and Mental Health Administration, National Institute of Mental Health, Psychopharmacology Research Branch, Division of Extramural Research Programs.

Huestis, M. A., & Choo, R. E. (2002). Drug abuse's smallest victims: in utero drug exposure. *Forensic Sci Int, 128*(1-2), 20-30.

Irner, T. B. (2012). Substance exposure in utero and developmental consequences in adolescence: A systematic review. *Child Neuropsychol, 18*(6), 521-549.

Jacobson, S. W., Jacobson, J. L., Sokol, R. J., Martier, S. S., & Ager, J. W. (1993). Prenatal alcohol exposure and infant information processing ability. *Child Dev, 64*(6), 1706-1721.

Johnson, J. L., & Leff, M. (1999). Children of substance abusers: overview of research findings. *Pediatrics, 103*(5 Pt 2), 1085-1099.

Kelley, S. J. (1992). Parenting stress and child maltreatment in drug-exposed children. *Child Abuse Negl, 16*(3), 317-328.

Lewis, B. A., Singer, L. T., Short, E. J., Minnes, S., Arendt, R., Weishampel, P., . . . Min, M. O. (2004). Four-year language outcomes of children exposed to cocaine in utero. *Neurotoxicol Teratol, 26*(5), 617-627.

Lidow, M. S., & Song, Z. M. (2001). Primates exposed to cocaine in utero display reduced density and number of cerebral cortical neurons. *J Comp Neurol, 435*(3), 263-275.

Malanga, C. J., & Kosofsky, B. E. (2003). Does drug abuse beget drug abuse? Behavioral analysis of addiction liability in animal models of prenatal drug exposure. *Brain Res Dev Brain Res, 147*(1-2), 47-57.

McLaughlin, K. A., Fox, N. A., Zeanah, C. H., & Nelson, C. A. (2011). Adverse rearing environments and neural development in children: the development of frontal electroencephalogram asymmetry. *Biological psychiatry, 70*(11), 1008-1015.

Minnes, S., Lang, A., & Singer, L. (2011). Prenatal tobacco, marijuana, stimulant, and opiate exposure: outcomes and practice implications. *Addict Sci Clin Pract, 6*(1), 57-70.

Nair, P., Black, M. M., Ackerman, J. P., Schuler, M. E., & Keane, V. A. (2008). Children's cognitive-behavioral functioning at age 6 and 7: prenatal drug exposure and caregiving environment. *Ambul Pediatr, 8*(3), 154-162.

O'Connor, M. J., Kogan, N., & Findlay, R. (2002). Prenatal alcohol exposure and attachment behavior in children. *Alcohol Clin Exp Res, 26*(10), 1592-1602.

Polen, M. R., Whitlock, E. P., Wisdom, J. P., Nygren, P., & Bougatsos, C. (2008) *Screening in Primary Care Settings for Illicit Drug Use: Staged Systematic Review for the United States Preventive Services Task Force*. Rockville (MD).

Pomeroy, E. C., & Steiker, L. H. (2012). Prevention and intervention on the care continuum. *Soc Work, 57*(2), 102-105.

Rivkin, M. J., Davis, P. E., Lemaster, J. L., Cabral, H. J., Warfield, S. K., Mulkern, R. V., . . . Frank, D. A. (2008). Volumetric MRI study of brain in children with intrauterine exposure to cocaine, alcohol, tobacco, and marijuana. *Pediatrics, 121*(4), 741-750.

Sheridan, M. A., Fox, N. A., Zeanah, C. H., McLaughlin, K. A., & Nelson, C. A., 3rd. (2012). Variation in neural development as a result of exposure to institutionalization early in childhood. *Proc Natl Acad Sci U S A, 109*(32), 12927-12932.

Simansky, K. J., & Kachelries, W. J. (1996). Prenatal exposure to cocaine selectively disrupts motor responding to D-amphetamine in young and mature rabbits. *Neuropharmacology, 35*(1), 71-78.

Smith, B. D., & Test, M. F. (2002). The risk of subsequent maltreatment allegations in families with substance-exposed infants. *Child Abuse Negl, 26*(1), 97-114.

Sowell, E. R., Mattson, S. N., Thompson, P. M., Jernigan, T. L., Riley, E. P., & Toga, A. W. (2001). Mapping callosal morphology and cognitive correlates: effects of heavy prenatal alcohol exposure. *Neurology, 57*(2), 235-244.

Steinhausen, H. C., Mas, S. D., Ledermann, C., & Metzke, C. W. (2006). Risk factors for the development of emotional and behavioural problems in children born to drug-dependent mothers. *Eur Child Adolesc Psychiatry, 15*(8), 460-466.

Sun, A. P., Freese, M. P., & Fitzgerald, M. (2007). An exploratory study of drug-exposed infants: case substantiation and subsequent child maltreatment. *Child Welfare, 86*(3), 33-50.

Svikis, D. S., & Reid-Quinones, K. (2003). Screening and prevention of alcohol and drug use disorders in women. *Obstet Gynecol Clin North Am, 30*(3), 447-468.

U.S. Department of Health and Human Services. (2011). Results from the 2010 National Survey on Drug Use and Health: Summary of National Findings. *NSDUH Series H-41, 11*(4658).

Williams, J. H., & Ross, L. (2007). Consequences of prenatal toxin exposure for mental health in children and adolescents: a systematic review. *Eur Child Adolesc Psychiatry, 16*(4), 243-253.

Table 1

Demographics and Clinical Characteristics

		Drug-Exposed (n=30)	Non-Drug Exposed (n=28)	p-value
Age (Mean and Standard Deviation, in years)		7.71 (3.077)	7.83 (3.715)	0.895
Sex	Male	23 (76.7%)	21 (75%)	X^2= 0.882
	Female	7 (23.3%)	7 (25%)	
Race	Caucasian	24 (80.0%)	20 (71.4%)	
	African-American	2 (6.7%)	2 (7.1%)	X^2= 0.832
	Bi-Racial	4 (13.3%)	2 (7.1%)	
	Unknown	0 (0.0%)	4 (14.2%)	
Socioeconomic Status (SES)		1.53 (0.819)	2.00 (1.018)	0.059
Number of Cases with the Following Family Status:				
	One biological parent in home	6 (20.0%)	11 (39.3%)	
	Two biological parents in home	1 (3.3%)	12 (42.9%)	
	Adopted	17 (56.7%)	0 (0%)	
	Foster Child	4 (13.3%)	0 (0%)	
	Other	2 (6.7%)	1 (3.6%)	
Number of Psychiatric Diagnoses		2.33 (1.061)	1.96 (1.071)	0.193
Number of Cases with the Following Diagnoses:				
	ADHD	21 (70.0%)	15 (53.6%)	0.204
	Oppositional Defiant Disorder	13 (43.3%)	10 (35.7%)	0.561
	Conduct Disorder	2 (6.7%)	1 (3.6%)	0.602
	Other Disruptive Behavior Disorders	3 (10.0%)	2 (7.1%)	0.705
	Autism Spectrum Disorders	5 (16.7%)	7 (25%)	0.443
	Post-Traumatic Stress Disorder	3 (10%)	1 (3.6%)	0.343
	Reactive Attachment Disorder	5 (16.7%)	0 (0%)	0.024*
	Anxiety Disorders	2 (6.7%)	7 (25.0%)	0.055
	Depressive Disorders	5 (16.7%)	4 (14.3%)	0.807
	Mental Retardation	2 (6.7%)	1 (3.6%)	0.602
	Learning Disorders	2 (6.7%)	1 (3.6%)	0.602
	Communication Disorders	6 (20.0%)	2 (7.1%)	0.161
Number of In Utero Exposed Drugs Classes		2.47 (0.937)	0.00 (0.000)	0.000*
Number of Cases with the Following In Utero Drug Exposure:				
	Opiates	4 (13.3%)		
	Benzodiazepines	3 (10.0%)		
	Tobacco	13 (43.3%)		
	Alcohol	17 (56.7%)		
	Marijuana	9 (30.0%)		
	Stimulants	18 (60.0%)		
	Polydrug Use	10 (33.3%)		

Table 1: Mean (Standard Deviation) reported for age, socioeconomic status, number of psychiatric diagnoses, and number of classes of drug exposures for both groups. Frequencies (percentage) also reported for number of children with each gender, race (comparison done on white vs. non-white), psychiatric diagnoses, and individual classes of drug exposures. P-values for each variable are presented based on independent samples t-tests. Outcomes marked with * indicate a significant group difference. SES is a rating determined by a combination of health insurance and parental employment; lower SES is coded with a lower score. Levels were low (1), lower-middle (2), middle (3), and high (4). Family status was coded as one biological parent (1), two biological parents (2), adopted (3), foster (4), and other (5). Abbreviation: ADHD attention-deficit/hyperactivity disorder.

Table 2

Clinical Outcomes			
	Drug-Exposed (n=30)	Non-Drug Exposed (n=28)	p-value
Baseline CGI-S Score	4.32 (0.670) [3-6]	4.00 (1.000) [3-6]	0.177
Final CGI-S Score	4.14 (0.803) [3-6]	3.57 (1.080) [1-6]	0.033*
Total Number of Outpatient Psychiatric Visits	6.50 (5.958) [1-22]	6.29 (3.430) [1-11]	0.869
Duration of Treatment (months) During Study Period	19.0(11.9) [1-36]	25.5 (11.2) [1-36]	0.06
Number of Psychotropic Medications at Clinic Intake	1.43 (1.357) [0-4]	1.14 (1.239) [0-4]	0.399
Number of Psychotropic Medications Used Throughout Clinic Treatment	3.53 (2.113) [1-8]	3.25 (1.756) [0-7]	0.582
Number of Psychotropic Medications Prescribed at the Last Study Visit	2.30 (1.264) [1-5]	1.64 (0.870) [0-4]	0.026*
Number of Medications Prescribed Throughout Lifetime	5.87 (3.839) [1-19]	4.11 (2.485) [0-10]	0.044*
Number of Atypical Antipsychotics Prescribed Throughout Lifetime	1.30 (1.264) [0-4]	0.86 (1.380) [0-5]	0.207
Number of Alpha Agonists Prescribed Throughout Lifetime	0.83 (0.791) [0-2]	0.50 (0.638) [0-2]	0.084
Number of Anti-Manic Agents Prescribed Throughout Lifetime	0.50 (1.167) [0-5]	0.14 (0.448) [0-2]	0.135
Number of Stimulants Prescribed Throughout Lifetime	1.60 (1.453) [0-4]	1.36 (1.496) [0-5]	0.533
Number of Antidepressants Prescribed Throughout Lifetime	1.00 (1.083) [0-4]	0.64 (0.780) [0-2]	0.158
Number of Typical Antipsychotics Prescribed Throughout Lifetime	0.03 (0.183) [0-1]	0.04 (0.189) [0-1]	0.961
Number of Anticholinergics Prescribed Throughout Lifetime	0.17 (0.461) [0-2]	0.11 (0.315) [0-1]	0.571
Number of Other Medications Prescribed Throughout Lifetime	0.43 (0.568) [0-2]	0.46 (0.637) [0-2]	0.846

Table 2: Mean (Standard Deviation) [Range] with p-values based on independent samples t-tests. Treatment related outcomes marked with * are significantly different between groups.

Table 3

Within Group Clinical Differences between Baseline and Last Visit

	Drug-Exposed (Difference	p-value)	Non-Drug Exposed (Difference	p-value)
CGI-S	0.179 (0.612)	0.134	0.435 (0.788)	0.015*
Total Number of Prescribed Medications	0.867 (1.502)	0.005*	0.500 (0.882)	0.006*
Atypical Antipsychotics	0.233 (0.430)	0.006*	0.071 (0.378)	0.326
Alpha Agonists	0.100 (0.403)	0.184	0.143 (0.448)	0.103
Anti-Manic Agents	-0.100 (0.305)	0.083	-0.036 (0.189)	0.326
Stimulants	0.400 (0.563)	0.001*	0.571 (0.790)	0.001*
Antidepressants	0.167 (0.461)	0.057	0.036 (0.429)	0.663
Typical Antipsychotics	[a]		[a]	
Anticholinergics	0.000 (0.263)	1.000	-0.071 (0.262)	0.161
Other	0.033 (0.414)	0.662	-0.036 (0.429)	0.663

Table 3: Mean (Standard Deviation) with p-values reported for within-group comparisons. Outcomes marked with * indicate a significant group difference.
[a]Cannot be calculated because the standard error of the difference is 0.

Table 4

Between Group Differences between Baseline and Last Visit		
	Drug-Exposed vs Non-Drug Exposed	p-value
CGI-S	0.256	0.197
Total Number of Prescribed Medications	0.367	0.266
Atypical Antipsychotics	0.162	0.135
Stimulants	0.171	0.343

Table 4: Mean Differences between drug-exposed and non-drug exposed groups, with p-values.